

Application No.: 09/526,802

Page 2

38. (New) A method for preparing a solid DHEA formulation, said method comprising:

mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph as determinable by solid state ¹³C NMR spectroscopy.

39. (New) A method for preparing a solid DHEA formulation, said method comprising:

mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), greater than 95% of which is present as the form I polymorph as determinable by solid state ¹³C NMR spectroscopy.

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 1-10 and 36-39 are pending with entry of this amendment, claims 11-35 being cancelled, and claims 36-39 being added herein. Cancellation of claims 11-35 is without prejudice, without intent to abandon any originally-claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing these cancelled claims.

This Amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. Support for the new claims can be found throughout the specification and the original claims at, for example, page 3, lines 19-23; page 4, lines 27-33; page 5, lines 8-30; page 7, line 20 through page 8, line 14; and page 16 line 18 through page 17, line 15.

Application No.: 09/526,802

Page 3

Election/Restriction.

Applicants thank the Examiner for reconsideration of the restriction requirement and respectfully note the partial recombination of the originally defined groups. Applicants herein confirm election of the combined claims of Group I (claims 1-4) and Group II (claims 5-10) as provided on page 2 of the Office Action. In addition, Applicants note that "Disposition of the Claims" provided on the Office Action Summary sheet reflects a typographical error as compared to the rejoinder provided by the Examiner. Specifically, while the Restriction Requirement mailed 10/4/2001 (and responded to on 11/5/2001) defines claims 5-10 as Group II, the Office Action Summary sheet notes only claims 5-8 and 10 of Group II as being pending. Furthermore, the Examiner refers to both "claims 5-8 and 10" and "claims 5-8 and 9" in the Office Action. Applicants therefore assume that these references to the Group II claims were inadvertent typographical errors on the part of the Office, particularly since claims 9 and 10 are drawn to related embodiments of the methods of the present invention (e.g., preparing a capsule versus preparing a tablet of the DHEA type I formulation) and were initially grouped together in the Restriction Response. If the rejoinder has been misunderstood, Applicants respectfully request clarification.

Pursuant to a restriction requirement made final, Applicants have cancelled claims 11-35 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

35 U.S.C. §103(a) Rejection.

Claims 1-8 and 10 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Morales et al. (USPN 5,407,927) and Loria (USPN 5,077,284) in combination with Chang et al. (1995 J. Pharm. Sci. 84:1169-1179). Applicants traverse.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P. § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must both be found in the prior art and not based on Applicant's disclosure. M.P.E.P. § 2143. Applicants submit that the rejection is improper because the Office Action has not met these three basic requirements.

Application No.: 09/526,802

Page 4

First, the Office Action does not establish how the cited art teaches the limitations of the claimed methods. Claim 1 is drawn to a pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient. The cited publications are alleged to teach formulations, methods and polymorphic forms of DHEA which encompass the subject invention. However, the publications alone or in combination do not teach the limitations of the claimed invention, e.g., a DHEA formulation having at least 85% DHEA form I.

Neither Morales nor Loria address the form of DHEA utilized in their formulations, and therefore do not teach or describe the use of at least 85% DHEA form I in a pharmaceutical formulation. The Chang publication is alleged to disclose solid state crystallization of DHEA and its polymorphs (e.g., forms I-III), but does not provide or enable production of a formulation having at least 85% DHEA form I. In particular, note the passage at page 5, lines 3-20 of Applicants' specification, which explains that Chang's supposedly pure form I was actually a mixture of form I and form VI. As summarized by Applicants in the specification at page 5, lines 17-22,

"Although conditions have been reported by others for preparing the above-mentioned stable forms (Chang et al., 1995), it has been found by the present applicants that previously reported methods for preparing form I, including those described by Chang, yield products *containing an additional polymorph that is designated herein as form VI*. Accordingly, improved methods described herein have been developed for preparing pure form I to the exclusion of other polymorphs." (emphasis added)

Chang was unaware that the DHEA form I preparations were contaminated with a previously unknown form, namely Form VI. The techniques used by Chang (differential scanning calorimetry and X-ray diffractometry) are unable to distinguish form I from the contaminating form VI. To prepare truly pure form I, the Applicants crystallized DHEA from 2-propanol, acetone, or acetonitrile, as described by Chang, and then carried out an additional step not performed by Chang. Specifically, this step entailed "suspending the precipitate from the first step in ethyl acetate (about 100 mL/30 g of DHEA) and stirring the resulting slurry at room temperature for about one week, followed by filtration." The Applicants confirmed the purity of this preparation by ¹³C-solid state NMR (¹³C-SSNMR) analysis, a technique not employed by Chang.

Thus, Chang does not provide the formulation of the present invention, nor does Chang provide the additional steps necessary to obtain a formulation comprising DHEA, at least

Application No.: 09/526,802

Page 5

85% of which is present as the form I polymorph and at least one pharmaceutical excipient. As such, the first requirement for establishing a *prima facie* case of obviousness has not been met, because the cited art does not teach or describe the limitations of the claimed invention.

Second, the Office Action has not articulated a specific motivation derived from the cited art to combine the cited art to achieve the formulation of the claimed invention. There must be evidence (other than speculation by the Office, or teachings from the specification) that one of ordinary skill in the art would have been motivated to make the modifications of the cited art necessary to arrive at the claimed invention (*In re Jones*, 958 F.2d 347, 21 USPQ2d 1941, 1944, Fed Cir. 1992). The assertions by the Office that a) one of skill in the art would have been "motivated to prepare additional beneficial preparations and formulations of DHEA" and that b) one of skill in the art "would expect the same results [from different polymorph formulations] because... it would be the same after dissolving in the solvent" do not provide a specific motivation to perform further purification steps on the Chang DHEA preparation. The additional sample handling step employed by Applicants in generating the at least 85% pure DHEA formulation is not even discussed in the cited art. In contrast, the Office has actually strengthened the Applicants' argument of non-obviousness since, upon inspection, the Office's statements are contradictory with one another. If the same results are to be expected regardless of the formulation, then there is no motivation for one of skill in the art to prepare "prepare additional beneficial preparations and formulations," much less the specific formulations of the subject invention.

With respect to the cited art, because Chang was not aware of the existence of form VI based upon the limited analytical methods employed, he cannot provide any motivation for further purifying the putative DHEA form I preparations to remove the contaminating form VI. Neither Morales nor Loria contemplate preparations of DHEA having >85% form I, nor do these publications provide motivation for using form I-specific formulations. Rather, the DHEA formulations provided by Morales and Loria performed adequately for the purposes set for in the respective publications. Thus, the second requirement for establishing a *prima facie* case of obviousness has not been met: there is no motivation provided by the cited art to generate the novel DHEA formulations of the present invention.

Regarding the third requirement for establishing obviousness, the Office Action has not shown that a combination of the cited art would lead to a reasonable expectation of success. Per

Application No.: 09/526,802

Page 6

MPEP § 2143, the expectation of success must be found in the prior art and cannot be based on Applicant's disclosure.

The Office Action states "It has been held that by changing the form, purity, or characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. *In re Cofer*, 53 CCPA (1966) 830, 354 F.2d 664, 668, 148 USPQ 268, 271." Applicants note that the form and/or purity of the DHEA formulation of the present invention is *not* inherent in or rendered obvious by the cited art; further manipulation of the DHEA sample (as provided by Applicant) is required to provide a sample of this polymorph composition and purity. Furthermore, the Office asserts that "different polymorphic forms are not patentable over each other in the absence of unexpected properties." However, Applicants submit that the formulations of the present invention do manifest unpredictable properties that differ from those in the cited art. For example, as noted in the specification at page 3, lines 11-16, differences in the polymorphic composition of the DHEA formulation lead to (often dramatic) variations in absorption, bioavailability and efficacy.

In the case of the form I polymorph, Chang suggested that the form I polymorph would have a higher bioavailability than forms II or III, based on data obtained using so-called "form I" DHEA preparations that, in fact, contained both form I and form VI. However, Applicants' specification demonstrates that form I DHEA is actually absorbed less rapidly and has a lower bioavailability than form II DHEA. Page 11, lines 15-18. As Applicants' specification indicates, this lower bioavailability of form I DHEA is accompanied by a higher stability as compared to form II, for example. Page 9, lines 2-3. Thus, Applicants' specification shows that the DHEA polymorphs exhibit differences in stability, absorption, and bioavailability and indicates that compositions containing different proportions of these polymorphs will have different properties. See, e.g., page 13, line 16 to page 14, line 4. Thus, the DHEA polymorph formulations of the present invention do manifest different properties than as taught in the cited art.

Cofer goes on to require that "the prior art suggest the particular structure or form of the compound or composition *as well as suitable methods of obtaining that structure or form*" for a finding of obviousness. Neither Morales nor Loria contemplate preparations of DHEA polymorphs, much less a DHEA formulation having >85% DHEA form I. Chang was not aware of the existence of DHEA form VI, and therefore necessarily lacks any guidance as to if or how production of a DHEA preparation having the claimed purity could be generated. *This guidance must be provided*

Application No.: 09/526,802

Page 7

by the cited art -- not Applicants' disclosure. Thus, the combination of the cited art does not provide a reasonable expectation of successfully producing pharmaceutical formulations comprising DHEA, at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient.

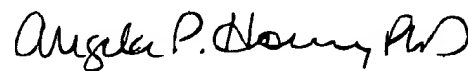
It is of course true (as stated in *Cofer*) that if the invention is not novel or non-obvious, it is not patentable. However, the Office cannot put the cart before the horse -- the Office must demonstrate how the cited art renders an invention obvious before one can come to the conclusion that it is unpatentable. This the Office has manifestly failed to do. The Office simply has not met the three basic requirements for establishing a *prima facie* case of obviousness. Applicants respectfully maintain that the claimed invention is not rendered unpatentable over Morales, Loria and Chang, because the cited references in combination do not teach the limitations of the claims, there is no motivation to combine the cited references, and there would not have been a reasonable expectation of successfully combining these references to achieve a particular result. The rejection is improper, and should be withdrawn.

CONCLUSION

Applicants respectfully submit that claims 1-10 and 36-39 are novel and nonobvious over the art. The foregoing amendments are believed to place the application in condition for allowance. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated. **In the event that any issues of substance are perceived to remain, Applicants request that the Examiner contact the undersigned to arrange for a telephonic interview, prior to preparation of any additional Office Action.**

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Application No.: 09/526,802

Page 8

APPENDIX A

**"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE
CLAIMS OF 09/526,802 WITH ENTRY OF THIS AMENDMENT**

1. A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient.
2. The formulation of claim 1, wherein at least 90% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
3. The formulation of claim 1, wherein at least 95% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
4. The formulation of claim 1, wherein at least 99% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
5. A method for preparing a solid DHEA formulation, said method comprising: mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph.
6. The method of claim 5, wherein at least 90% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
7. The method of claim 5, wherein at least 95% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
8. The method of claim 5, wherein at least 99% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.
9. The method of claim 5, further comprising the step of placing the solid formulation into a capsular container suitable for delivery to the gastrointestinal tract.
10. The method of claim 5, further comprising the step of compressing the solid formulation to form a tablet.
- 11 to 35. (Cancelled)

Application No.: 09/526,802

Page 9

36. (New) A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph as determinable by solid state ^{13}C NMR spectroscopy, and at least one pharmaceutical excipient.

37. (New) A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), greater than 95% of which is present as the form I polymorph as determinable by solid state ^{13}C NMR spectroscopy, and at least one pharmaceutical excipient.

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